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TITLE: The Johns Hopkins RTR Consortium: A Collaborative Approach to Advance Translational Science and Standardize Clinical Monitoring of Restorative Transplantation

PRINCIPAL INVESTIGATOR: W. P. Andrew Lee, MD

CONTRACTING ORGANIZATION: Johns Hopkins University  
Baltimore, MD 21218

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| 6. AUTHOR(S)<br>W. P. Andrew Lee, MD and Gerald Brandacher, MD<br><br>E-Mail: wpal@jhmi.edu                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |              |                          |                            | 5d. PROJECT NUMBER                            |                                           |
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| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)<br>Johns Hopkins University<br>733 N. Broadway<br>Suite 117<br>Baltimore, MD 21205                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |              |                          |                            | 8. PERFORMING ORGANIZATION REPORT NUMBER      |                                           |
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| 13. SUPPLEMENTARY NOTES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |              |                          |                            |                                               |                                           |
| 14. ABSTRACT<br>The <b>overall goal</b> for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners. The Consortium has thus assembled three complimentary, multidisciplinary research projects from Johns Hopkins, Massachusetts General Hospital and University of Pittsburgh. Each of the individual projects has made significant progress during this reporting period. The Initiating Site through their coordinated efforts has facilitated that all projects are mostly on track with the proposed statements of work. The group has met all Major Tasks for Year 2, in particular we have assisted sites with ACURO and HRPO submissions, contacted sites to remind them of upcoming Quarterly Report deadlines, Collected and Reviewed Quarterly Reports and held update calls to discuss progress among project leaders. |              |                          |                            |                                               |                                           |
| 15. SUBJECT TERMS<br>Vascularized Composite Allotransplantation, Immunoregulation, Tolerance Rejection, Ischemia Reperfusion<br>Cell based Therapy, Large animal models, Allograft, Hand Transplantation ,Face Transplantation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |              |                          |                            |                                               |                                           |
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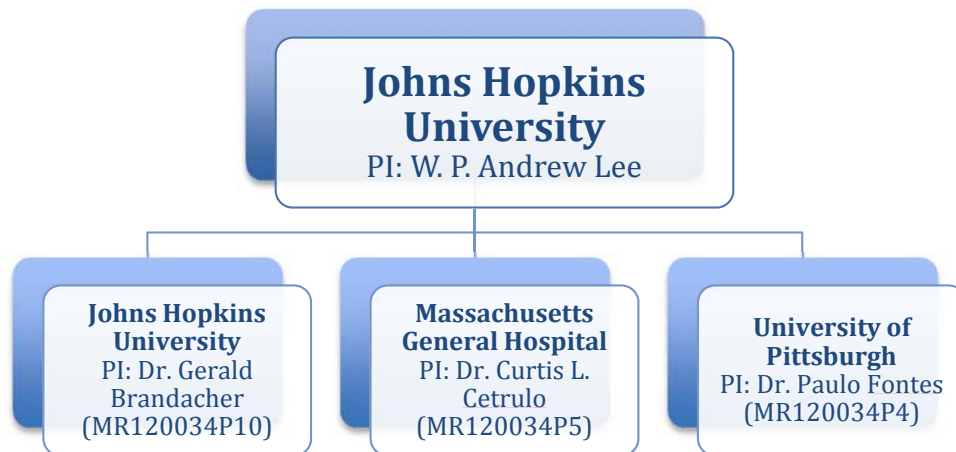
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## 1. INTRODUCTION

Restorative Transplantation has emerged as a new modality to restore both function and form following devastating injuries to the face and upper extremities in a way not previously possible. Despite initial success, great challenges remain in ameliorating long-term immunosuppression, understanding acute and chronic rejection, and optimizing immune monitoring and perioperative protocols. As the field of Restorative Transplantation matures, significant opportunities are emerging for transplant researchers and clinicians to capitalize on the unique features of VCA, glean from advances and experience in solid organ transplantation (SOT), and achieve genuine progress in transplant outcome and patient safety. **The Johns Hopkins RTR Consortium** has thus *assembled some of the world's most renowned scientists, researchers, and surgeons in vascularized composite allotransplantation (VCA) research to address some of the most relevant and pressing research areas in reconstructive transplantation.*

The **overall goal** for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners. The **central hypothesis** is that the maturing field of Restorative Transplantation will benefit the most from the establishment of a multi-institutional, multi-disciplinary collaborative consortium that builds on knowledge and experience derived from the study of SOT to address the unique challenges and opportunities presented in this new field.



## 2. KEYWORDS

Vascularized Composite Allotransplantation  
Immunoregulation  
Tolerance  
Rejection  
Ischemia Reperfusion  
Cell based Therapy  
Large animal models  
Allograft  
Hand Transplantation  
Face Transplantation

## 3. ACCOMPLISHMENTS

The Initiating Site has met all Major Tasks for Year 2 as outlined in the Statement of Work. In particular, we have assisted sites with ACURO and HRPO submissions, contacted sites to remind them of upcoming Quarterly Report deadlines, Collected and Reviewed Quarterly Reports and held update calls to discuss progress among project leaders.

The accomplishments for each of the individual projects are outlined below:

### **Johns Hopkins University (MR120034P10)**

During the current reporting period the group continue to study a belatacept-based protocol to enable calcineurin inhibitor (CNI) minimization/avoidance (Aim 1) after heterotopic swine hind-limb allotransplantation across a full SLA mismatch and furthermore set out to examine the efficacy of transitioning to belatacept (CTLA4-Ig) maintenance therapy from a calcineurin inhibitor based immunosuppression regimen (Aim 2).

In year 2 of the study, all animals in Aim 1 and 2 have undergone successful transplantation. All group I animals died prematurely due to infectious complications related to high dose tacrolimus treatment. 2/3 animals that received sub-therapeutic tacrolimus (group II) have rejected their grafts. 3/5 animals that received belatacept in addition to low dose tacrolimus (group III) have achieved long-term graft survival (>230 days). All group IV and V animals that received 60 days of tacrolimus and proceeded to either weaning immunosuppression or transition to belatacept have not shown evidence of rejection thus far. Overall, these preliminary results indicate that belatacept is highly effective as a biologic agent in maintaining allograft survival without the need for conventional high dose CNI based immunosuppression. Furthermore, the long-term graft survival off of immunosuppression for animals treated with low dose tacrolimus suggest that the vascularized bone component of the composite graft may have a robust immunomodulatory effect. Additional clinical follow-up and *in vitro* experiments are ongoing to characterize the immune status of the current recipients.

Overall the results obtained during year 2 are highly encouraging and indicate that CTLA4-Ig has the ability to both allow for CNI minimization after VCA as well as to maintain rejection free allograft survival after weaning and complete withdrawal of CNI in patients who have already undergone VCA. This could allow to develop alternative protocols devoid of the well known and documented toxicities and side effects of CNIs which are currently hampering broader application of these life changing reconstructive modalities.

#### **Massachusetts General Hospital (MR120034P5)**

The investigators have developed a NHP upper extremity transplantation model, and during this reporting period have commenced work utilizing this model to the investigation of delayed induction of transplant tolerance. Specifically during the second year of this award the investigators have optimized the delayed tolerance induction protocol in non-human primates. By reducing the delay period from the original 4 months to 2 months, the group is confident that the number of acute rejection episodes can be minimized or eliminated completely even. This is particularly pertinent in view of their previous experiments where acute rejection led to irreversible VCA loss. In addition, decreasing the delay period will also reduce the overall duration of exposure to high-dose immunosuppression and the attendant risks of related complications such as PTLD and cachexia, which can lead to irreversible weight loss and premature termination of the experiment.

In addition, the team has optimized the heterotopic partial face transplant procedure in non-human primates. Following the unfortunate loss of M6914 after recovering from anesthesia, the group has implemented closer, invasive intra-operative monitoring of blood pressure through the placement of an intraarterial line in the femoral artery. Aggressive peri-operative preparation in the form of irradiated whole blood from the exsanguinated donor and recipient-typed blood from other experimental animals has ensured that blood transfusions are readily available as necessary for intra-operative support.

#### **University of Pittsburgh (MR120034P4)**

During this reporting period the group has provided proof-of-concept pre-clinical experiments in a porcine model which very important to determine the role of MP as a new modality for CTA preservation. The investigators were able to reproduce the successful findings published from their liver experience in a similar MP/HBOC system utilized over a 9 hour period.

The MP/HBOC system as a new option for CTA preservation displayed the same safety and effectiveness seen in the solid organ model. The reported experiments were based on a very challenging model involving 14 hours of CTA preservation followed by graft implantation and the subsequent follow up of the transplant recipients under triple immunosuppressive therapy. The control group VRAM grafts were preserved within the

current standard of care (CSP) and showed moderate to severe IRIs with massive necrosis within the first post-operative week.

The MP-treated VRAM grafts had a significantly better outcome, based on the lower magnitude of the IRIs, lower degree of inflammation and additional signs of advantageous metabolic features regarding oxidative stress, fuel utilization and protein synthesis. The new Limb Assist® device will be utilized on a follow up DOD project (MR140030) led by LtCol Michael Davis, MD, FACS, USAF, MC in the Institute for Surgical Research, San Antonio, TX.

The proposed specific aims were fully achieved as summarized below:

1. The MP/HOBC system promoted an increased CIT period without any damage to the VRAM graft during preservation
2. The MP/HBOC system minimized the IRIs observed during preservation when compared to the current standard of care (CSP).
3. The MP/HBOC system had a positive impact on the immune profile of the VRAM grafts, where a significantly lower degree of inflammation was observed after preservation. This should have a major impact in long-term studies where the lesions acquired from IRIs would have a lower degree of alloactivation and most likely a lower degree of both acute and chronic rejection.

**a. What were the major goals of the project?**

The **overall goal** for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners.

**b. What was accomplished under these goals?**

Each of the individual projects has made significant progress as detailed above. The Initiating Site through their coordinated efforts has facilitated that all projects are mostly on track with the proposed statements of work.

**c. What opportunities for training and professional development has the project provided?**

Nothing to Report.

**d. How were the results disseminated to communities of interest?**

Nothing to Report

- e. **What do you plan to do during the next reporting period to accomplish the goals?**

We will continue our coordinated efforts and increase the frequency of project leader conference calls to ensure timely completion of the tasks as outlined in the statement of work.

**4. IMPACT:**

- a. **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report

- b. **What was the impact on other disciplines?**

Nothing to report

- c. **What was the impact on technology transfer?**

Nothing to report

- d. **What was the impact on society beyond science and technology?**

Nothing to report

**CHANGES/PROBLEMS:**

- a. **Changes in approach and reasons for change**

Nothing to report.

- b. **Actual or anticipated problems or delays and actions or plans to resolve them**

Nothing to report.

- c. **Changes that had a significant impact on expenditures**

Nothing to report.

- d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

- d. **Significant changes in use or care of human subjects**



Nothing to report.

**e. Significant changes in use or care of vertebrate animals.**

Nothing to report.

**f. Significant changes in use of biohazards and/or select agents**

Nothing to report.

**5. PRODUCTS**

Nothing to report.

**6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**a. What individuals have worked on the project?**

Name: W. P. Andrew Lee

Project Role: Principal Investigator

Nearest Person Month Worked: 5% (0.6 calendar months)

Contribution to Project:

Name: Gerald Brandacher

Project Role: Co-Investigator

Nearest Person Month Worked: 5% (0.6 calendar months)

Contribution to Project:

Name: Rochelle Smith

Project Role: Assistant Grant Administrator

Nearest Person Month Worked: 40% (4.8 months)

Contribution to Project: Rochelle Smith drafts reminder emails to send to each site prior to report submission deadlines, coordinates with the PIs to obtain updated information, maintains financial records, and oversees project progress with the Scientific Director and PI.

**b. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to Report

**c. Partnering Organization**

**Johns Hopkins University (MR120034P10)**

Gerald Brandacher, MD

Johns Hopkins University  
Baltimore, Maryland

**Massachusetts General Hospital (MR120034P5)**

Curtis L. Cetrulo, MD  
Massachusetts General Hospital  
Boston, Massachusetts

**University of Pittsburgh (MR120034P4)**

Paulo Fontes, MD  
University of Pittsburgh  
Pittsburgh, PA

**d. SPECIAL REPORTING REQUIREMENTS**

a. **QUAD CHARTS:** Attached.

**e. APPENDICES**

Nothing to Report.

# The Johns Hopkins RTR Consortium: A Collaborative Approach to Advance Translational Science and Standardize Clinical Monitoring of Restorative Transplantation

MR120034, Restorative Transplantation Research

Award Number: W81XWH-13-2-0059

PI: W. P. Andrew Lee, M.D.

Org: Johns Hopkins University, School of Medicine Award Amount: \$286,298

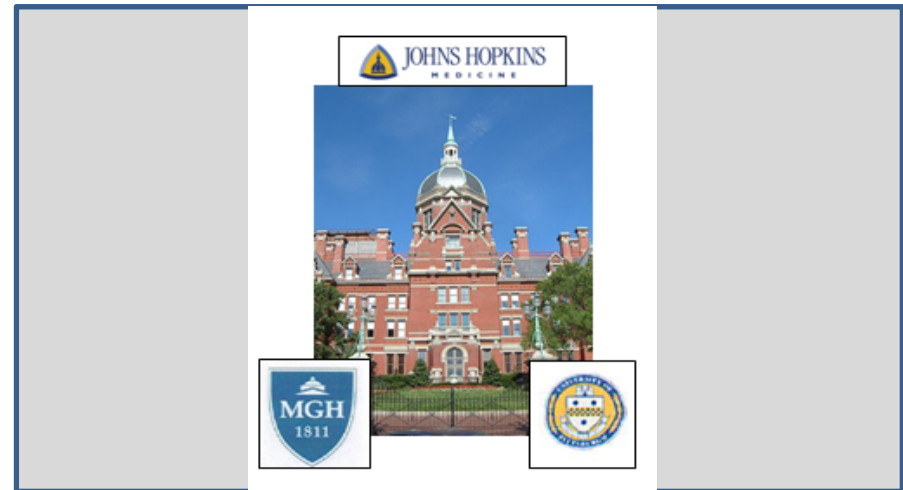


## Study/Product Aim(s)

- Establishing monthly contact with sites during Year 1 of grant to facilitate communication and annual report generation.
- Continuing monthly contact with sites during Year 2 of grant to facilitate communication and annual report generation.
- Continuing monthly contact with sites during Year 3 of grant to facilitate communication and final report generation.

## Approach

The purpose of this administrative core is to coordinate the efforts of the collaborating sites in order to ensure timely meeting of project aims and milestones while facilitating site communications with the sponsor.



Accomplishment: Implementation of Departmental Clinical Research Core and basic sciences support to enable intra- and inter-institutional research collaborations and perform grant management for both commercial and federal sponsors.

## Timeline and Cost

| Activities                                                                                                              | CY | 14              | 15              | 16              |
|-------------------------------------------------------------------------------------------------------------------------|----|-----------------|-----------------|-----------------|
| Establishing monthly contact with sites during Year 1 of grant to facilitate communication and annual report generation |    |                 |                 |                 |
| Continuing monthly contact with sites during Year 2 of grant to facilitate communication and annual report generation   |    |                 |                 |                 |
| Continuing monthly contact with sites during Year 3 of grant to facilitate communication and final report generation.   |    |                 |                 |                 |
| <b>Estimated Budget (\$K)</b>                                                                                           |    | <b>\$93,790</b> | <b>\$95,558</b> | <b>\$96,950</b> |

Updated: October 15, 2015

## Goals/Milestones

### CY14 Goals

- ✓ Collect & Review Consortium Quarterly Reports
- ✓ Conference Calls with Consortium Sites
- ✓ Milestone: Local IRB/IACUC Approval & HRPO/ACURO Approval

### CY15 Goals

- ✓ Collect & Review Consortium Quarterly Reports
- ✓ Conference Calls with Consortium Sites
- ✓ Milestone: Local IRB/IACUC Continuing Review Approval
- ✓ Milestone: HRPO/ACURO Continuing Review Approval

### CY16 Goals

- ☐ Collect & Review Consortium Quarterly Reports
- ☐ Conference Calls with Consortium Sites
- ☐ Complete and submit final Consortium Report to Sponsor
- ☐ Milestone: Local IRB/IACUC Continuing Review Approval
- ☐ Milestone: HRPO/ACURO Continuing Review Approval

### Comments/Challenges/Issues/Concerns

- N/A

### Budget Expenditure to Date

Projected Expenditure: N/A

Actual Expenditure: \$170,440.80